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Pharmacoeconomics in nephrology: considerations on cost-effectiveness of screening for albuminuria

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study by Palmer *et al.* from the viewpoint of pharmacoeconomic science.

Introduction

In this issue, Palmer *et al.* [1] demonstrate that screening for nephropathy in hypertensive type 2 diabetic patients and subsequent treatment with renoprotective antihypertensive agents may result in excellent value for money from the US health care perspective. Estimated costs and effects were combined in a cost-utility analysis, to express the incremental costs per quality-adjusted life year (QALY) for add-on treatment of the angiotensin receptor blocker (ARB) irbesartan after detection of nephropathy through screening, compared with conventional antihypertensive treatment only, in the absence of screening. Nephropathy was defined as microalbuminuria or nephropathy; i.e. urine albumin excretion (UAE) $>20 \mu\text{g}/\text{min}$ (corresponding to a UAE expressed per 24 h $> 30 \text{ mg}/24 \text{ h}$, with $>300 \text{ mg}/24 \text{ h}$ generally defining nephropathy). Such screening and subsequent ARB treatment—add on to conventional antihypertensive therapy—was estimated to result in favourable clinical outcomes with only marginally increasing overall costs. Furthermore, estimated incremental cost-effectiveness was well below a willingness to pay (WTP) threshold of US\$50 000 per QALY for the USA [2]. Despite the fact that such an absolute quantitative threshold for costs per QALY has to be interpreted with caution by decision-makers in health care systems, the exact cost-per-QALY ratio found by the authors at US\$20 011 per QALY gained and an estimated 77% probability of being below this US\$50 000 threshold certainly suggest a favourable pharmacoeconomic profile [1,3]. Palmer *et al.* used a Markov model to simulate the progression from a healthy state to end-stage renal diseases (ESRDs) and second-order Monte Carlo simulation—both ‘state-of-the-art’ mathematical techniques in pharmacoeconomics—to account for multiple parameter uncertainty and to derive results as listed above [3,4]. In this editorial, we discuss the

How to conduct a pharmacoeconomic analysis?

Pharmacoeconomics is defined as the science focusing on scarcity of budgets for pharmacotherapeutic interventions; i.e. that part of health economics with the focus on pharmacotherapy. Cost-effectiveness and cost-utility analysis are the main instruments used in pharmacoeconomics. Cost-effectiveness analyses relate differences between monetary costs and benefits (net costs) of an intervention to a clinical outcome, such as blood-pressure lowering, serious events avoided or life-years gained. In cost-utility analyses, net costs of an intervention are related to gains in quality of life and life years gained (including the quality of those years), both expressed and aggregated in QALYs [3]. As such, a QALY integrates gains in survival and gains in quality during life. For the reimbursement of new drugs—such as ARBs in the last decade—currently in many countries pharmacoeconomic research is required and the outcome of it should indicate that a new drug is ‘cost-effective’ (i.e. below a certain predefined, or thought, threshold for net costs per outcome considered, usually life-year gained or QALY gained). Examples in nephrology in recent years exist next to ARBs: for example, are sorafenib and sunitinib cost-effective enough in the treatment of renal cell carcinoma to justify their reimbursement?

Also, such pharmacoeconomic analyses should adhere to guidelines for the conduct of such studies, guaranteeing a minimum quality level. These guidelines are globally rather uniform and some of them warrant some remarks here. Firstly, full economic evaluations should ideally be performed from the societal perspective. The societal perspective typically includes indirect non-medical costs of production losses, next to direct medical costs [5]. Secondly, these analyses should include all short- and long-term costs and effects. Ideally, a lifelong perspective is applied. Therefore, long-term analyses are now required to support drug reimbursement decisions or implementation of large-scale interventions, such as screening or vaccination programs. Despite sophisticated methods developed and used for economic analyses on short-term clinical studies, such analyses are often considered to be insufficient,

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given the lack of a long-term perspective. Thirdly, long-term perspectives—beyond clinical-trial horizons—require the use of adequate modelling techniques, such as Markov models. Markov models generally enable the analysis of transitions from one health state (for example, microalbuminuria) to another (for example, nephropathy), within a framework of a predefined number of such health states. In the model, quality of life is generally defined per state; durations of stay in these states can easily be analysed over long time frames.

Palmer *et al.* [1] developed a Markov model to simulate disease progression over a 25-year time frame approximating a lifetime perspective, even more so, as a discount rate at 3% for money and health gains was applied, following US-guidelines. In pharmacoeconomic analysis, costs, savings and health gains are discounted to account for time preference; i.e. one prefers to receive an amount of money now rather than receiving that same amount of money in the future, or one prefers to pay costs in the future over paying the same amount now (a similar reasoning is assumed for health). So, pharmacoeconomists attach different values or utilities to amounts of money or life years that occur on different moments/periods in time: the higher the discount rate, the lower the value that is attached to costs, benefits and health gains that occur in the (distant) future. Recent discussions have focused on the appropriateness of using similar discount rates for money and health, for example with regard to discounting life years [6]. Following that discussion, the Netherlands recently changed its pharmacoeconomic guideline on discounting to differential discounting: 4% for money and 1.5% for health. Generally, differential discounting—i.e. relatively low discounting of health compared with money—favours preventive interventions with health gains in the (distant) future, inclusive screening programs such as those on albuminuria.

Cost-effectiveness of RAAS-intervening agents in type 2 diabetic patients

We recently reviewed within-trial analytical and Markov-model based economic evaluations of Renine Angiotensine Aldosterone System (RAAS)-intervening agents in type 2 diabetic patients [7], including those studies used by Palmer *et al.* [1]: RENAAL, IDNT, IRMA-2 and BENEDICT [8–11]. Economic outcomes from these studies generally suggest that treatment with RAAS-intervening agents in type 2 diabetic patients, with overt or incipient nephropathy, confers health gains and net cost-savings compared with conventional (non-RAAS) treatment [7,12]. In particular, delay of renal disease may confer relevant cost-savings in terms of ESRD, dialyses and kidney transplantations averted. Additionally, it has been shown that benefits can be expected in reducing cardiovascular events [7].

Favourable pharmacoeconomic outcomes for treatment may justify screening, to identify those who may benefit from such treatment. Thus, Palmer *et al.* [1] argue that screening for albuminuria in the specific population of hypertensive type 2 diabetic patients and subsequent start of renoprotective ARB treatment in those found positive will

result in excellent value for money. It is still difficult to definitely assess the relative therapeutic values of ARBs in relation to ACE inhibitors. Indications exist to show that ACE-inhibitor treatment results in similar beneficial effects on renal disease progression and occurrence of cardiovascular events as ARBs, both in type 2 diabetic patients as well as in non-diabetic patients [11,13,14]. Except for the DETAIL-trial, however, there are no nephrological studies comparing the effectiveness of ACE inhibitors and ARBs on a head-to-head basis for specific nephrological endpoints [14]. Indirect comparison of both classes of drugs is also difficult. Most trials with ACE inhibitors are partially placebo-controlled, often with, as a result, better blood pressure control in the ACE inhibitor groups, whereas most ARB trials showed comparable blood pressure control in the experimental and control groups [7,13]. Indirect comparisons are therefore likely to favour ACE-inhibitors over ARBs.

One study simulated cost-effectiveness of universal ACE-inhibitor treatment for type 2 diabetic patients—irrespective of both blood pressure and albuminuria levels—and found this to be highly cost-effective [15]. So, beyond discussions on screening for albuminuria in type 2 diabetic patients, universal treatment of such patients with RAAS-intervening agents is already under consideration. On the one hand, this will save screening costs, and on the other hand drug costs will increase, which is particularly relevant if drugs are used prior to patent expiry. Obviously, the topic warrants further pharmacoeconomic analysis, including exploring the impact of price reductions as the first ACE inhibitors are now becoming off-patent, enhancing the economic profile of these agents.

Cost-effectiveness of screening in the general population

Economic evaluation based on the outcomes of the IDNT study in combination with the IRMA-2 study previously showed that ARB-treatment results in higher cost-savings if applied in the early stage of microalbuminuria compared with late overt diabetic nephropathy, both in US and European settings [16]. This suggests that the earlier the treatment is started, the better it is for hypertensive type 2 diabetic patients. Would this also apply for the non-diabetic population with albuminuria? Should we screen for microalbuminuria (UAE > 30 mg/24 h) and/or nephropathy (UAE > 300 mg/24 h) in this population as well, and would this be cost-effective? The PREVEND (Prevention of Renal and Vascular ENd stage Disease) study, as well as other studies, showed that microalbuminuria (UAE > 30 mg/24 h) presents an independent risk-factor for renal disease and cardiovascular events, also in the non-diabetic population [17]. As long as all effects in terms of renal and cardiovascular outcomes and proper cost estimates are considered, there are certainly indications that albuminuria-based 'test-and-treat' strategies could be a successful tool, resulting in a reduced number of renal and cardiovascular outcomes and possibly a favourable cost-effectiveness [18–20].

Boulware *et al.* [18] estimated that annual screening for dipstick proteinuria by general practitioners may be cost-effective to prevent ESRD in the US setting, except if limited to only elderly or hypertensive persons. However, large groups of normotensive and non-elderly groups remain, with net costs per QALY estimates that are generally considered not cost-effective. Previously, however, we argued that several rather study-specific factors determine these negative results [19]. In particular, (i) the general practitioner setting may be unnecessarily expensive and much cheaper screening might be achieved if subjects are requested to send a first morning void urine sample by post to a central laboratory, as done in the PREVEND study, or using other potentially efficient ways such as dipstick self-tests; (ii) the yield of the screening might be relevantly increased if instead of only proteinuric, microalbuminuric persons are also treated and (iii) inclusion of beneficial effects of RAAS treatment on cardiovascular events—next to ESRD—will relevantly enhance cost-effectiveness.

As a part of the observational PREVEND-study, a randomized clinical trial was undertaken (PREVEND-IT: Prevention of Renal and Vascular ENstage Disease Intervention Trial), in which fosinopril treatment was shown to result in a statistically significant reduction in albuminuria and a strong trend towards significant difference in cardiovascular outcomes in a non-diabetic, albuminuric and primarily normotensive population [20]. The PREVEND-IT economic evaluation indicated a favourable cost-effectiveness of screening for high-normal albuminuria (UAE > 15 mg/24 h) and subsequent treatment with the ACE inhibitor fosinopril to prevent cardiovascular events [20]. This indicates that—next to screening in specific patient populations, such as hypertensive type 2 diabetic patients—screening of the general population for albuminuria could be a cost-effective strategy. Such a strategy is beneficial to prevent cardiovascular events in (micro)albuminuric persons, whereas it may be expected to prevent ESRD especially in macroalbuminuric persons. Thus, nephrological profit in albuminuria levels and ESRD is obtained in the slipstream of cardiovascular disease prevention.

Conclusion

In conclusion, favourable economic profiles in treatment of type 2 diabetic patients with nephropathy were found for ARBs. This favourable profile justifies screening for nephropathy and subsequent ARB treatment. As early treatment (starting in the stage of microalbuminuria) was found to be economically superior to late treatment (starting in the stage of overt nephropathy), a strong case exists for screening for albuminuria in diabetic type 2 patients and subsequent treatment. Possibly, this effect might be extrapolated to ACE inhibitors. In fact, for ACE inhibitors, universal treatment of all type 2 diabetic patients has even been suggested as cost-effective. For a decision on whether to prefer ARBs or ACE inhibitors, head-to-head trials are needed or at least sound indirect comparisons—comparing the effectiveness of both types of agents with non-RAAS-intervening agents at similar blood pressure control.

Further research is needed to explore the benefits of screening for albuminuria in the non-diabetic general population, and the corresponding economic profile of such a screening. For example, results on favourable cost-effectiveness from the Dutch PREVEND study require confirmation in other settings. Next to renal disease, it is important to include benefits of screening and treatment on cardiovascular events in such cost-effectiveness analyses.

Conflict of interest statement. None declared.

(See related article by A. J. Palmer *et al.* A health economic analysis of screening and optimal treatment of nephropathy in patients with type 2 diabetes and hypertension in the USA. *Nephrol Dial Transplant* 2008; 23: 1216–1223.)

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